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Design and synthesis of a new polymer-supported Evans-type oxazolidinone: an efficient chiral auxiliary in the solid-phase asymmetric alkylation reactions

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Abstract—Wang resin-supported Evans' chiral auxiliary (**23**) was designed based on a novel polymer-anchoring strategy, which utilizes the 5-position of the oxazolidinone ring, and its new synthetic route applicable to multi-gram preparation in just a day was developed. Solid-phase Evans' asymmetric alkylation on **23**-derived *N*-acylimide resin and following lithium hydroperoxide-mediated chemoselective hydrolysis afforded the corresponding α-branched carboxylic acids in desired high stereoselectivities (up to 97% ee) and moderate to good overall yield (up to 70%, for 3 steps), which were comparable to those of the conventional solution-phase methods. Furthermore, recovery and recycling of the polymer-supported chiral auxiliary were successfully achieved without decreasing the stereoselectivity of the product. Therefore, this is the first successful example that the solid-phase Evans' asymmetric enolate-alkylation was efficiently performed on the solid-support, and it is concluded that the connection to the solid-support via the 5-position of the oxazolidinone ring is an ideal strategy in the solid-phase Evans' chiral auxiliary.

1. Introduction

Evans' chiral oxazolidinone is one of the efficient auxiliaries for preparing chiral building blocks necessary to synthesize molecules possessing the accurate spatial configuration of specific functional groups.[1,2] Its generality and reliability with high optical purity have already been established in a variety of efficient asymmetric syntheses of low molecular weight chiral compounds and complicated natural products.[3–5] Moreover, its potential is expanding in the study of novel asymmetric reactions.[6]

Solid-phase organic synthesis has been developed as a rapid and diversified method in organic chemistry.[7] As compared to solution-phase, the solid-phase technology provides a simple procedure 'filtration' for rapidly achieving the isolation of desired compounds or recovering expensive reagents or catalysts attached onto the solid-support for recycling. Hence, many useful reagents or catalysts, especially those used in chiral synthesis, in solution-phase methods have been intensively and successfully applied to the solid-phase methods so far.[8] However, some solid-supported chiral auxiliaries are problematic in achieving high quality of stereoselective reactions.[9] One of such well-known examples is pseudoephedrine[10] grafted onto the Merrifield resin. This solid-supported auxiliary showed lower stereoselectivity in asymmetric alkylation (approx. 85% ee) in comparison to the corresponding solution-phase experiments.

Evans' oxazolidinone has also been applied to the solid-phase stereoselective reactions such as enolate-alkylation reaction,[11] aldol reaction,[12] Diels–Alder cycloaddition[13] and 1,3-dipolar cycloaddition.[14] However, undesired results similar to those observed in the solid-supported pseudoephedrine case were reported, especially in the fundamental solid-phase asymmetric enolate-alkylation reaction which prepares optically active α-branched carboxylic acid derivatives.[11b] Indeed, maximum stereoselectivity was 90% ee in asymmetric benzylation using the auxiliary resin **1** (Fig. 1A).[15] Moreover, a side reaction was reported in the preparation of solid-supported L-serine derived chiral oxazolidinone **2**.[16] Therefore, to improve the efficiency in stereoselective reactions, we previously reported a

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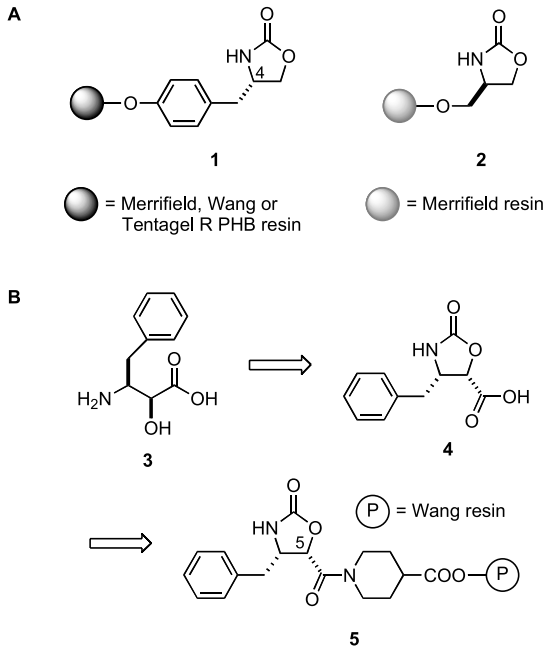


Figure 1. Reported polymer-supported Evans' chiral auxiliaries anchored at the 4-position of the oxazolidinone ring (A) and design of a new auxiliary anchored at the 5-position (B).

polymer-supported chiral Evans' oxazolidinone with a novel anchoring system onto the solid-support as a rapid communication.[17] In this article, we describe the detailed design and synthesis of the polymer-supported chiral Evans' oxazolidinone and its reusability in Evans' asymmetric alkylation.

2. Results and discussion

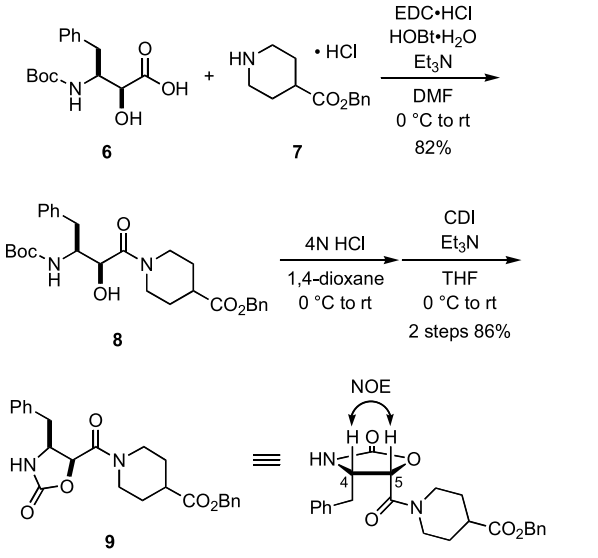
2.1. Design of a new polymer-supported chiral oxazolidinone

One of the common features of polymer-supported Evans' chiral auxiliary in all previous reports[11–14] is that a chiral 4-substituted oxazolidin-2-one was connected to the solid-support through the chiral discriminating moiety at the 4-position of the oxazolidinone ring (Fig. 1A). This made us suspect that chiral control ability of Evans' oxazolidinone is influenced by the polystyrene backbone of the solid-support, leading to the low stereoselectivity in the asymmetric alkylation.[11b] Hence, we proposed an alternative anchoring strategy, which leaves the crucial chiral discriminating moiety unmodified, and utilizes the external 5-position for connecting to the solid-support (Fig. 1B).

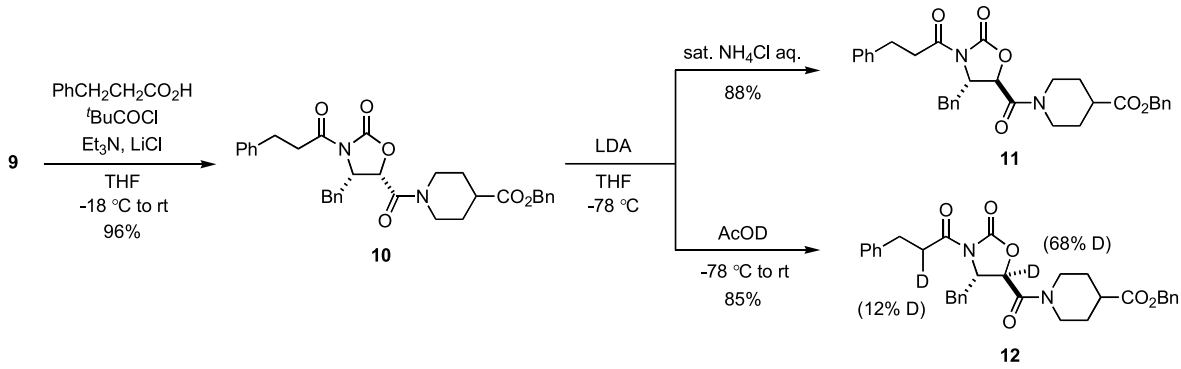
To prepare such a new oxazolidinone derivative, we focused on α-hydroxy-β-amino acids, which are routinely used in our laboratory as a core structure for the development of effective aspartic protease inhibitors.[18] The unique structure of α-hydroxy-β-amino acids, in which three different functional groups, i.e. amino, hydroxyl and carboxyl groups, are located on two adjacent asymmetric carbon atoms gave us the idea. Namely, the known oxazolidinone formation[19] at the 1,2-amino alcohol moiety of α-hydroxy-β-amino acid, (2*S*,3*S*)-3-amino-2-hydroxy-4-phenylbutanoic acid **3** (allophenylnorstatine, Apns),[18] can afford a desired oxazolidinone derivative **4** with a benzyl substituent at the 4-position as a chiral discriminating group and a free carboxyl group at the 5-position which can connect with the solid-support (Fig. 1B). In addition, Burgess et al. pointed out that Wang resin had a better enantiomeric excess than Merrifield resin in asymmetric benzylation.[11b] Since Wang resin has an additional benzyl moiety which has a space from the polystyrene backbone in comparison to Merrifield resin, we planned to employ both Wang resin and, as a further spacer, a piperidine-4-carboxylic acid. Thus, in the designed solid-supported auxiliary **5**, this spacer is connected to the carboxyl group at the 5-position of the oxazolidinone moiety by a tertiary-amide bond and to Wang resin by an ester bond. This tertiary-amide bond with no amide proton is stable under both acidic and basic conditions. The ester bond between the spacer and Wang resin can be formed by the standard methods.

2.2. Evaluation of new oxazolidinone derivatives in solution-phase model experiment

To understand the efficacy of designed solid-support chiral oxazolidinone **5** as a new chiral auxiliary, we first studied a solution-phase experiment, using a model oxazolidinone derivative **9** whose C-terminal is protected by a benzyl ester to mimic Wang resin. As Scheme 1 shows, **9** was synthesized by a three-step reaction. Namely, Boc-Apns-OH **6** was coupled to benzyl piperidine-4-carboxylate **7**[20] by the EDC–HOBt (EDC: 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide, HOBt: 1-hydroxybenzotriazole) method[21] to give dipeptide **8**,[22] followed by the removal of the Boc group and CDI (1,1′-carbonyldiimidazole) treatment[19] to afford the *cis*-configured oxazolidinone derivative **9** as a single isomer. During the cyclization reaction, neither aziridine nor 1,2-imidazoylamine byproduct formation was observed.[23] The *cis*-configuration of **9** was confirmed by the coupling constant[24] between H-4 and H-5, and NOE experiments (Scheme 1 and Ref. 25). Synthesized **9** had



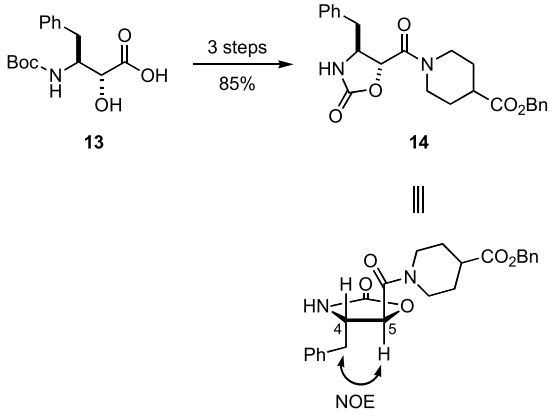
Scheme 1. Synthesis of a *cis*-configured oxazolidinone derivative **9** from Boc-Apns-OH **6**.



Scheme 2. Epimerization and deuterium incorporation to the *cis*-configured carboximide **9**.

coupling constants of $J_{4,5}=7.9$, 8.1 Hz, which corresponded to the representative value of the *cis*-configured oxazolidinone.

Next, oxazolidinone **9** was *N*-acylated with 3-phenylpropionic acid by the mixed anhydride method to obtain carboximide **10** (Scheme 2).[26] Although there are three α-protons in **10**, the newly introduced carboximide α-proton was expected to be most acidic. Since it was reported that the imide-selective enolization of substrates with the both carboximide and ester structures was accomplished by careful base addition,[27] and that after asymmetric reaction, *N*-acyl fragments were selectively cleaved from the auxiliary by the imide-specific lithium hydroperoxide-mediated hydrolysis,[28] we proposed **9** as a chiral auxiliary that could be recovered and reused. However, its enolate formation gave a new compound even with a careful addition of LDA (1.2 equiv) to the cooled THF solution of **10** and a subsequent stirring for 0.5 h. This compound was an epimerized *trans*-configured carboximide **11**.[29] This result suggests that the α-proton of the carboxamide moiety was predominantly deprotonated by LDA to diminish the steric repulsion caused by *cis*-configuration.[30] Indeed, quenching lithium enolate generated in situ from **10** with acetic acid-*d* (99at.% D) afforded the deuterized **12** in 85% yield. The deuterium was incorporated mainly at the α-position of the carboxamide moiety (68% D) along with the α-position of the *N*-acylimide moiety (12% D).



Scheme 3. Synthesis of a *trans*-configured oxazolidinone derivative **14** from Boc-Pns-OH **13**.

This unexpected result prompted us to suggest that stable *trans*-configured oxazolidinone **14** was suitable for the auxiliary (Scheme 3). We synthesized **14** according to the procedure shown in Scheme 1, starting from Boc-Pns-OH **13** (Pns: phenylnorstatine), a 2*R* isomer of **6**, in 85% yield (3 steps). The relative stereochemistry of **14** was analyzed by NMR. Coupling constants of $J_{4,5}$ were 5.1 and 5.3 Hz, which are well consistent with the known value in *trans*-configuration[24] and a strong NOE signal was observed between H-5 and two protons at the benzylic position.[25] In addition, the most stable conformation of **14** obtained from conformational analysis showed a dihedral angle of 136.4° between two methine hydrogens (H-4 and H-5). This value and Karplus curve reasonably supported the observed coupling constant. From these observations, the configuration between H-4 and H-5 in **14** was confirmed as *trans*. Furthermore, the absolute stereochemistry of **14** was confirmed as 4*S*,5*R* by the X-ray crystal structural analysis of (*R*)-phenylethylamide **15**[31] derived from **14** (Fig. 2). In addition, it was found that the piperidine-4-carboxylic acid spacer extended outside from the oxazolidinone core, suggesting that this spacer does not interfere with the asymmetric reaction.

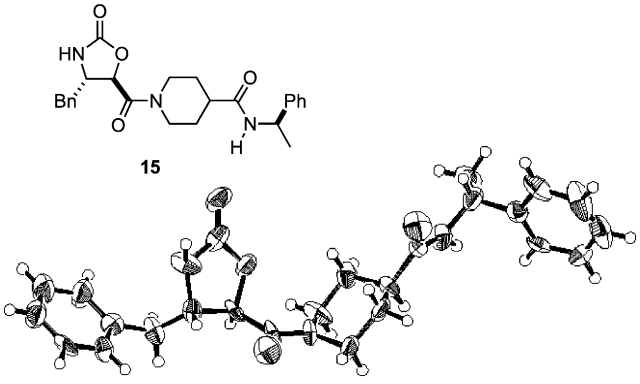
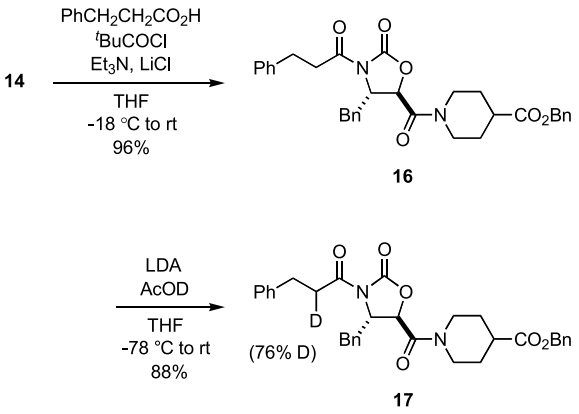


Figure 2. X-ray crystal structure of (*R*)-phenylethylamide **15**.

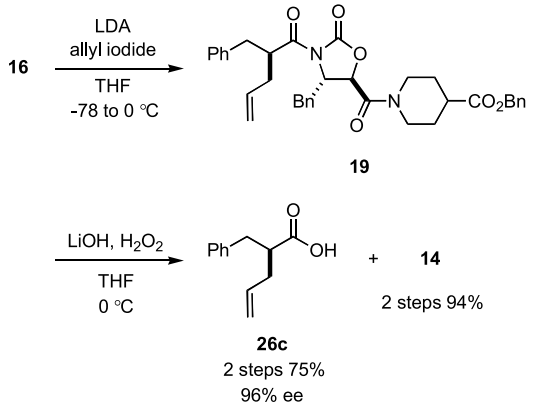
Next, we synthesized *N*-3-phenylpropionylated oxazolidinone **16** and subjected it to the deuterium labeling to confirm the enolization position (Scheme 4) by the same procedure described in Scheme 2. No particular change on TLC was observed during the enolization and the recovered product (88% yield) contained 76% of deuterized **17**, exclusively at the α-position of the desired carboximide moiety with unmodified **16**. This result suggests that the



Scheme 4. Deuterium incorporation to *trans*-configured carboximide **16**.

α-position of the imide *N*-acyl moiety in **16** has the most acidic α-proton, which is predominantly deprotonated by LDA. Self-condensation of **16** was not observed under this reaction condition.

With these positive observations, we examined the Evans' asymmetric allylation of the carboximide **16** as a model for alkylation (Scheme 5).[15] Briefly, to a solution of **16** in THF was added LDA (1.2 equiv) dropwise at −78 °C. After stirring for 0.5 h, the generated *Z*-*O*-enolate **18**[32] was treated with allyl iodide (3.0 equiv), and the temperature of the reaction mixture was gradually increased up to 0 °C over a period of 3 h. Resultant **19** was hydrolyzed by LiOOH without any purification.[28] The desired α-allylated carboxylic acid **26c** was obtained in good yield (2 steps 75%, an average of 87% for each of the two steps in the reaction sequence) and high stereoselectivity (96% ee),[33] which were comparable to the standard Evans' asymmetric allylation in solution-phase.[15] Oxazolidinone **14** was sufficiently recovered (94%) without epimerization, and no byproduct produced by the endocyclic cleavage of the oxazolidinone ring[28] was observed. These results proved that the *trans*-configured oxazolidinone **14** was effective as a chiral auxiliary and that the spacer moiety did not interfere with the asymmetric reaction.



Scheme 5. Asymmetric allylation of the *N*-3-phenylpropionylated carboximide **16**.

An energy minimization study of enolate intermediate **18** suggested that its conformation corresponds to that of the original chelation-controlled model proposed for standard Evans' chiral auxiliary system (Fig. 3).[15,34] Interestingly, this modeling also suggested that nucleophilic attack of the hydroperoxide anion to the oxazolidinone carbonyl for the endocyclic cleavage is effectively obstructed by the steric effect of the benzyl and carboxamide moieties.[35] From these data, we selected the structure of **14** originating from Pns as the candidate for solid-supported Evans' auxiliary.

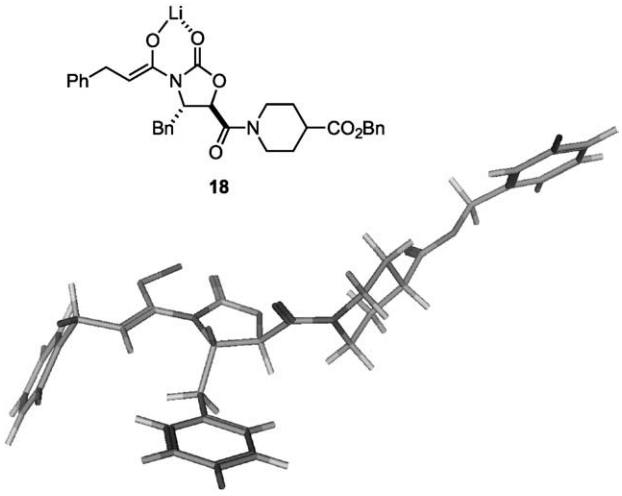


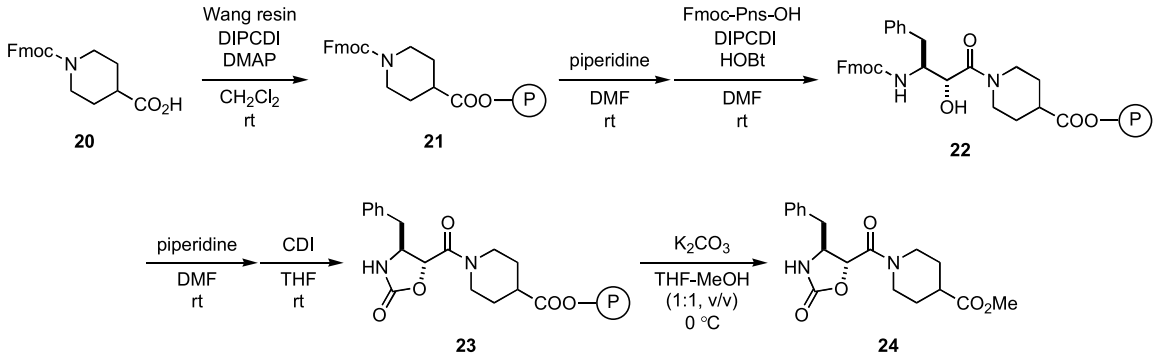
Figure 3. Energy minimization study of enolate intermediate **18**.

2.3. Solid-phase synthesis of Wang resin-supported chiral oxazolidinone 23

In our previous communication,[17] Wang resin-supported chiral oxazolidinone **23** was obtained by the carbodiimide-mediated coupling between Wang resin and the oxazolidinone-spacer unit prepared from **14** by hydrogenolysis. Since four-step solution-phase synthesis of this unit and its excess use (4 equiv) required for complete loading onto the resin were inefficient, in the present study we developed a more convenient synthetic route for **23** using Fmoc-based solid-phase method as shown in Scheme 6.[36] Namely, Fmoc-piperidine-4-carboxylic acid **20** was first loaded to Wang resin using the DIPCDI–DMAP (DIPCDI: 1,3-diisopropylcarbodiimide) method[37] in CH_2Cl_2. After Fmoc-deprotection of **21** with 20% piperidine, Fmoc-Pns-OH was coupled by the DIPCDI–HOBt method to give the dipeptide resin **22** followed by removal of the Fmoc group. The resultant 1,2-amino alcohol moiety was converted to oxazolidinone with CDI. Methanolysis of **23** with potassium carbonate in anhydrous THF–MeOH yielded the corresponding methyl ester **24** as a single isomer (95% for 6 steps). During this synthesis, neither epimerization at the 5-position nor byproduct formation such as aziridine and 1,2-aminoimidazole was observed.[23] It is noteworthy that all reactions in Scheme 6 proceeded smoothly at room temperature within a few hours, and multi-gram quantity of the oxazolidinone resin **23** with high loading yield was efficiently synthesized in just a day.

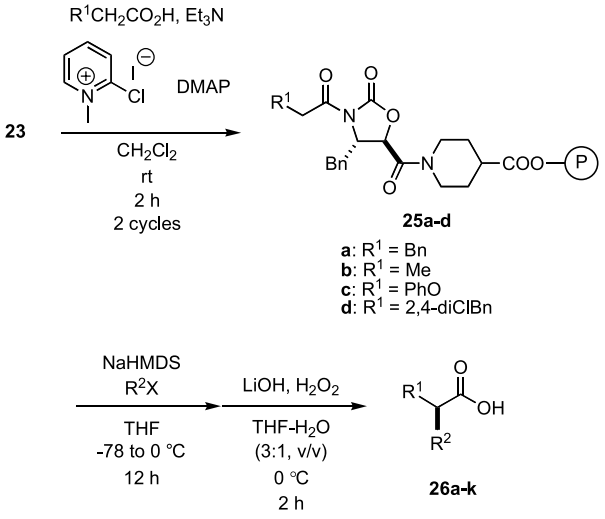
2.4. Solid-phase Evans' asymmetric alkylation with the oxazolidinone resin 23

At first, we investigated the solid-phase Evans' asymmetric allylation of the *N*-3-phenylpropionylated carboximide



Scheme 6. Solid-phase synthesis of Wang resin-supported oxazolidinone resin **23**.

resin **25a**, which was prepared from **23** by Mukaiyama method (Scheme 7).[38] It was found that the use of NaHMDS (3 equiv) as a base and gradual increase of the temperature of reaction mixture up to 0 °C over a period of 12 h in the alkylation reaction were quite effective.[39] After quenching the reaction mixture with saturated NH_4Cl aq, the allylated carboximide resin was recovered, washed, then subjected to the LiOOH-mediated hydrolysis. The desired chiral α-allylated carboxylic acid **26c** was obtained with high stereoselectivity (96% ee), which was equal to the model experiment in solution-phase (Table 1, entry 3). The absolute configuration of acid **26c** was determined in comparison to the reported specific rotation,[33] suggesting



Scheme 7. Solid-phase asymmetric Evans' alkylation.

that the asymmetric alkylation on resin **25a** also proceeded in the same chelation-controlled model as the solution-phase method.[15] During the hydrolytic cleavage, the ester linkage and oxazolidinone core were stable.[40] These encouraging results urged us to understand the generality of **23** in the Evans' asymmetric alkylation reaction. Several carboximide resins **25b–d** were prepared and subjected to the similar solid-phase alkylation reactions with a series of electrophiles (R^2X).[41] The results are summarized in Table 1. Favorably, not only highly reactive alkyl halides such as MeI and BnBr but also less reactive EtI reacted sufficiently under the same reaction conditions. Hydrolytic cleavage of the resultant resin afforded the corresponding chiral α-branched carboxylic acids **26a–k** with satisfying isolated yields (50–70%, for 3 steps) and enantiomeric excesses (84–97% ee).[42] Especially, in the asymmetric benzylation of carboximide resin **25b**, stereoselectivity was found to be 97% ee (Table 1, entry 6), which was better than the value reported by Burgess et al.,[11b] and was as high enough as in the corresponding solution-phase asymmetric alkylation utilizing the standard chiral 4-substituted oxazolidin-2-one.[15] The relatively lower yield was due to the fact that the yield includes the three-step process from the oxazolidinone resin **23** to the final alkylated product **26**. We consider that yield for two steps (alkylation and hydrolysis) is similar to that of the solution-phase method, and average yield calculated for each step was reasonably acceptable (79–89%). We assume that these successful results are attributed to our new polymer-anchoring strategy based on the connection at the 5-position of the oxazolidinone ring. This liberates the chiral differentiating benzyl group from the polystyrene backbone of the resin, freeing the auxiliary

Table 1. Results of the solid-phase asymmetric Evans' alkylations

Entry	25	R^1	R^2X	26	Yield[a] (%)	ee[b] (%)
1	**25a**	Bn-	MeI	**26a**	61(85)	85
2	**25a**	Bn-	EtI	**26b**	50(79)	88
3	**25a**	Bn-	Allyl-I	**26c**	68(88)	96
4	**25a**	Bn-	Propargyl-Br	**26d**	62(85)	96
5	**25a**	Bn-	$BrCH_2CO_2Et$	**26e**	62(85)	92
6	**25b**	Me-	BnBr	**26f**	70(89)	97
7	**25b**	Me-	4-BrBnBr	**26g**	68(88)	97
8	**25b**	Me-	4-NO_2BnBr	**26h**	55(82)	97
9	**25b**	Me-	2,4-diClBnI	**26i**	65(87)	97
10	**25c**	PhO-	Allyl-I	**26j**	50(79)	96
11	**25d**	2,4-diClBn-	MeI	**26k**	59(84)	84

[a] Combined yield of 3 steps starting from oxazolidinone resin **23**. Value in the parenthesis is the average yield for each step.
[b] Determined by chiral HPLC analysis after conversion to the corresponding (*S*)-α-methylbenzylamine-derived amides.

unit from the solid-support, which was not realized in the previous system based on the 4-position anchoring.

2.5. Recycling of the Wang resin-supported auxiliary 23

The recycling of the expensive auxiliary is one of the key points in the development of the polymer-supported chiral auxiliary. However, the recycling of the polymer-supported Evans' oxazolidinone has been reported in only one case of solid-phase 1,3-dipolar-cycloaddition,[14b] with a considerable reduction of regio- and stereo-selectivity depending on the cycle number up to three, although the reason was unclear.

Hence, the ability of recycling of the Wang resin-supported chiral auxiliary **23** was studied in the solid-phase asymmetric allylation, mentioned above, to obtain α-allylated carboxylic acid **26c** (Fig. 4). After the first cycle of allylation, the recovered chiral auxiliary resin **23** was washed and dried, then *N*-acylation with 3-phenylpropionic acid gave the corresponding carboximide resin **25a** again. After the continuous second to fourth solid-phase asymmetric allylation, the desired product **26c** was obtained in high enantioselectivity (96% ee each) (Table 2). Throughout these cycles, the product's stereoselectivity was maintained successfully, although the yield gradually decreased about

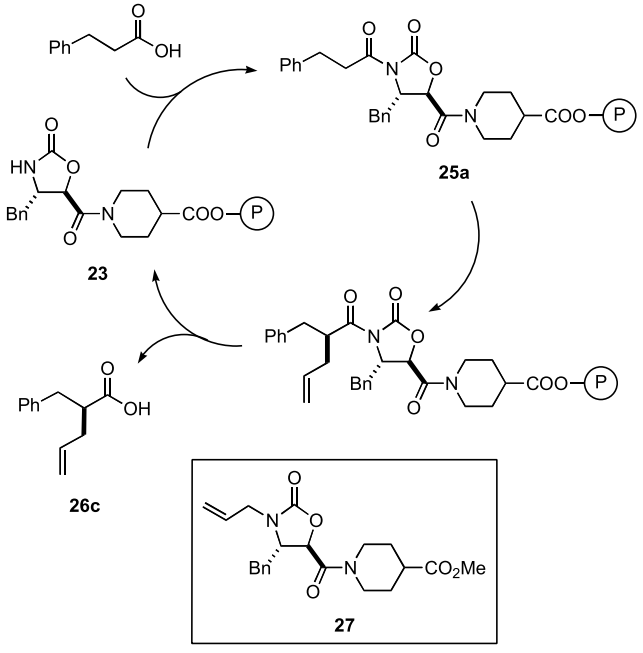


Figure 4. Recycling of the chiral auxiliary resin **23**.

Table 2. Recycling of the Wang resin-supported chiral oxazolidinone **23** in Evans' asymmetric allylation

Cycle	Yield[a] (%)	ee[b] (%)
1	68	96
2	59	96
3	49	96
4	42	96

[a] Combined yield of 3 steps starting from oxazolidinone resin **23**.
[b] Determined by chiral HPLC analysis after conversion to the corresponding (*S*)-α-phenylethylamides.

8% in each cycle. After the fourth cycle, the resin was cleaved by methanolysis to measure the amount of the residual auxiliary. Methyl ester **24**, which corresponds to the chiral auxiliary on the resin, was obtained in 71% yield along with the 22% of undesired *N*-allylated oxazolidinone **27**.[43] This indicated that the reduced yield obtained after recycling was due to the formation of byproduct **27**, in which the substrate-loading site was completely blocked by the allyl group (Fig. 4). It is thought that this unfavorable side reaction was induced by the partial elimination of the *N*-acyl moiety during enolate-alkylation steps. In fact, from detailed analysis of our solution-phase model experiment, 6% of *N*-allylated byproduct formation was detected. Therefore, the reaction conditions should be carefully adjusted to minimize unfavorable *N*-alkylation of the oxazolidinone resin.

3. Conclusion

In the development of an efficient tool to prepare versatile chiral synthon, we designed and synthesized Wang resin-supported Evans' chiral oxazolidinone derivative based on the novel polymer-anchoring strategy, which utilizes the 5-position of the oxazolidinone ring. Solid-phase asymmetric Evans' enolate-alkylation reaction on this auxiliary resin proceeded successfully and a series of chiral α-branched carboxylic acids was obtained in high stereoselectivities (up to 97% ee), which are parallel to those obtained in the comparative classical solution-phase experiments. Therefore, this is the first successful example that Evans' asymmetric alkylation reaction proceeded efficiently on a solid-support. Furthermore, recycling of this polymer-bound chiral auxiliary was achieved by maintaining stereoselectivity of the product. This newly developed solid-support auxiliary provides a variety of chiral α-branched carboxylic acid derivatives, which would be valuable synthetic building blocks in Medicinal Chemistry.[44] These results also suggest the significance of the polymer-anchoring strategy of chiral auxiliary to perform the satisfactory asymmetric induction in solid-phase organic synthesis. Further application studies to other solid-phase Evans' asymmetric reactions are now in progress.

4. Experimental

4.1. General

NMR spectra (^{1}H and ^{13}C) were recorded on a JEOL JNM-AL300 (^{1}H: 300 MHz; ^{13}C:75.5 MHz) or a Varian UNITY INOVA 400NB (^{1}H: 400 MHz; ^{13}C: 100 MHz) spectrometer and the chemical shift values were expressed in parts per million downfield from tetramethylsilane (TMS) as an internal standard. All coupling constants (*J* values) were reported in Hertz (Hz). Infrared (IR) spectra were recorded using a Shimadzu FT-IR-8300 Fourier Transform Infrared Spectrophotometer. Melting points were taken on a micro hot-stage apparatus (Yanagimoto) and were uncorrected. Mass spectra (MS) were obtained by electron impact (EI) ionization methods on JEOL GCmate MS-BU20. Elemental analyses were done on a Perkin–Elmer Series

CHNS/O Analyzer 2400. Specific rotations were recorded on a Horiba High-speed Accurate Polarimeter SEPA-300 with a sodium lamp and are reported as follows: $[\alpha]_D^T$ (c g/100 mL, solvent). The enantiomeric excess was determined by chiral HPLC analysis with JASCO HPLC systems consisting of the following: pump, 880-PU; detector, 875-UV, measured at 230 nm; column, Chiralcel® OD normal phase column (4.6×250 mm; Daicel Chemical Ind., Ltd, Tokyo, Japan); mobile phase, *n*-hexane/EtOH; flow rate, 1.0 mL/min. Solvents used for HPLC analysis were of HPLC grade. Organic extracts were dried over sodium sulfate (Na_2SO_4), filtered, and concentrated using a rotary evaporator at <40 °C bath temperature. Solids and involatile oils were vacuum dried at <2 mmHg. Solution- and solid-phase asymmetric alkylation reactions were carried out under Ar atmosphere, using anhydrous THF in flame-dried glassware. In the case of solid-phase asymmetric alkylation reactions, immobilized substrates were agitated by a slow stirring under Ar atmosphere.

4.2. Materials

Commercially available chemicals were obtained from Wako Pure Chemical Industries, Ltd (Osaka, Japan), Nacalai Tesque, Inc. (Kyoto, Japan), Aldrich Chemical Co., Inc. (Milwaukee, WI) and Tokyo Kasei Kogyo Co., Ltd (Tokyo, Japan), and used without further purification. Exceptionally, triethylamine was distilled from CaH_2 under Ar atmosphere and stored over KOH (pellet). Dehydrated MeOH and THF were purchased from Kanto Chemical Co., Inc. (Tokyo, Japan) and stored over pre-activated pellet-type molecular sieves 3A and 4A, respectively. Wang resin (0.80 mmol/g, styrene–1%DVB, 200–400 mesh) was purchased from Watanabe Chem. Ind., Ltd (Hiroshima, Japan). Boc-Apns-OH and H-Pns-OH were purchased from Nippon Kayaku (Tokyo, Japan). Boc- and Fmoc-Pns-OH were prepared from H-Pns-OH by the standard procedure. NaHMDS was used as supplied (Aldrich) as a solution in THF (1.0 M). Column chromatography was carried on Merck 107734 silica gel 60 (70–230 mesh). Analytical thin layer chromatography (TLC) was performed using Merck 105715 silica gel 60 F_{254} precoated plates (0.25 mm thickness) and compounds were visualized by UV illumination (254 nm) and by heating after dipping in 10% ethanolic solution of phosphomolybdic acid or after spraying ca. 0.7% ethanolic solution of ninhydrin. Preparative TLC was done with Merck 105717 silica gel 60 F_{254} plate (2.0 mm thickness).

4.3. Synthesis of *cis*-configured oxazolidinone 9 and *N*-3-phenylpropionylated carboximide 10

4.3.1. Benzyl *N*-{(2*S*,3*S*)-3-[(*tert*-butoxycarbonyl)-amino]-2-hydroxy-4-phenylbutanoyl}piperidine-4-carboxylate 8. To a solution of Boc-Apns-OH **6** (4.0 g, 13.5 mmol), benzyl piperidine-4-carboxylate HCl **7** (4.1 g, 16.2 mmol) and HOBt·H_2O (7.7 g, 16.2 mmol) in DMF (68 mL) was added EDC·HCl (3.1 g, 16.2 mmol) in parts at 0 °C. After stirring for 0.5 h at the same temperature, Et_3N (7.0 mL, 16.2 mmol) was added dropwise, then the reaction mixture was stirred overnight at room temperature. The solution was diluted with AcOEt and washed consecutively with 5% citric acid aq, 5% $NaHCO_3$ aq, water (×2) and brine. After the organic layer was dried over Na_2SO_4, the solvent was removed under reduced pressure. The resulting white powder **8** (5.5 g, 82%) was used for the next reaction without any purification. $R_f=0.44$ (*n*-hexane/AcOEt=1:1); mp 37–39 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.14 (m, 10H), 5.16, 5.13 (2d, 0.5×2H, $J=12.3$ Hz), 5.12 (s, 0.5×2H), 5.06 (br d, 0.5H, $J=8.4$ Hz), 5.02 (br d, 0.5H, $J=9.0$ Hz), 4.58 (d, 0.5H, $J=2.2$ Hz), 4.55 (d, 0.5H, $J=2.2$ Hz), 4.22–3.92 (m, 4H), 3.14, 3.06 (2ddd, 0.5×2H, $J=13.7$, 11.2, 3.1 Hz), 2.88, 2.54 (2ddd, 0.5×2H, $J=13.4$, 11.2, 3.1 Hz, partially overlapping with the next signal), 2.71–2.51 (m, 3H), 2.08–1.21 (m, 4H), 1.38 (s, 0.5×9H), 1.37 (s, 0.5×9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.5, 173.5, 169.9, 169.6, 155.6, 137.8, 135.7, 129.2, 129.1, 128.6, 128.4, 128.3, 128.2, 128.1, 126.5, 126.4, 79.6, 77.2, 69.9, 69.8, 66.5, 54.1, 53.4, 44.1, 42.0, 42.0, 40.7, 34.4, 34.2, 28.3, 27.6; $[\alpha]_D^{26}=+16.3$ (c 0.64, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 3690, 3441, 3038, 1728, 1699, 1639, 1497, 1367, 1238, 1169, 698 cm^{-1}; HRMS (EI): found M^+ 496.2576, $C_{28}H_{36}N_2O_6$ requires M^+ 496.2573. Anal. Calcd for $C_{28}H_{36}N_2O_6$: C, 67.72; H, 7.31; N, 5.64; found: C, 67.69; H, 7.46; N, 5.58.

4.3.2. Benzyl *N*-[(4*S*,5*S*)-4-benzyl-1,3-oxazolidin-2-one-5-carbonyl]piperidine-4-carboxylate 9. Compound **8** (5.4 g, 10.9 mmol) was treated with 4 M HCl/dioxane (45.0 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 2.5 h. After the solvent was removed under reduced pressure, the obtained colorless oil was dissolved in anhydrous THF (110 mL). To this solution was added Et_3N (2.3 mL, 16.4 mmol) dropwise at 0 °C, followed by CDI (2.7 g, 16.4 mmol). The cloudy reaction mixture was stirred overnight at room temperature, diluted with AcOEt, and washed consecutively with 5% citric acid aq, 5% $NaHCO_3$ aq, water and brine. After the organic layer was dried over Na_2SO_4, the solvent was removed under reduced pressure and the residue was applied to silica-gel column chromatography (*n*-hexane/AcOEt=1:10) to yield **9** as a white powder (4.0 g, 86% for 2 steps). $R_f=0.27$ (*n*-hexane/AcOEt=1:10); mp 136–137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.14 (m, 10H), 5.41 (d, 0.5H, $J=7.9$ Hz), 5.39 (d, 0.5H, $J=8.1$ Hz), 5.15 (s, 0.5×2H), 5.14 (s, 0.5×2H), 4.98 (br s, 0.5H), 4.92 (br s, 0.5H), 4.46, 4.23 (2dtd, 0.5×2H, $J=13.6$, 4.0,1.5 Hz, partially overlapping with the next signal), 4.28–4.18 (m, 1H), 3.76 (m, 0.5×2H), 3.25, 3.11 (2ddd, 0.5×2H, $J=13.6$, 10.3,3.3 Hz), 2.92–2.53 (m, 3H), 2.87–2.71 (m, 0.5×2H, partially overlapping with the next signal), 2.05–1.93 (m, 2H), 1.80–1.62 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.4, 173.4, 163.8, 163.7, 157.4, 157.3, 135.8, 135.6, 129.2, 129.1, 129.1, 128.9, 128.6, 128.4, 128.1, 127.3, 127.2, 75.1, 74.9, 66.5, 55.5, 55.4, 44.1, 43.9, 41.5, 41.2, 40.8, 40.0, 37.4, 37.3, 28.1, 28.1, 27.6, 27.4; $[\alpha]_D^{25}=-58.4$ (c 1.01, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 3030, 3020, 1774, 1730, 1666, 1231, 1207, 800, 791, 768, 714, 675 cm^{-1}; HRMS (EI): found M^+ 422.1843, $C_{24}H_{26}N_2O_5$ requires M^+ 422.1841. Anal. Calcd for $C_{24}H_{26}N_2O_5$: C, 68.23; H, 6.20; N, 6.63; found: C, 68.14; H, 6.28; N, 6.49.

4.3.3. Benzyl *N*-[(4*S*,5*S*)-4-benzyl-(3-phenylpropionyl)-1,3-oxazolidin-2-one-5-carbonyl]piperidine-4-carboxylate 10. To a solution of 3-phenylpropionic acid (1.8 g, 11.7 mmol) in anhydrous THF (30 mL) was added Et_3N

(3.1 mL, 22.5 mmol) and trimethylacetylchloride (1.3 mL, 10.8 mmol) dropwise at −18 °C. The reaction mixture was stirred at the same temperature for 0.5 h, then anhydrous LiCl (420 mg, 9.9 mmol) was added, followed by the slow addition of a solution of oxazolidinone **9** (3.8 g, 9.0 mmol) in anhydrous THF (20 mL). After the addition was completed, the reaction mixture was stirred overnight at room temperature. The solution was poured into ice-cold satd $NaHCO_3$ aq and the organic phase was extracted with AcOEt, washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting oil was applied to silica-gel column chromatography (*n*-hexane/AcOEt=4:1) to yield the desired compound **10** as a white solid (4.7 g, 95%). R_f= 0.48 (*n*-hexane/AcOEt=1:1); mp 153–155 °C; ^{1}H NMR (400 MHz, $CDCl_3$). Major isomer δ 7.41–7.04 (m, 15H), 5.11–5.09 (m, 1H), 5.07 (s, 2H), 4.92–4.87 (m, 1H), 4.36–4.33 (m, 1H), 3.36–3.26 (m, 2H), 3.11–2.93 (m, 6H), 2.22 (tt, 1H, J=11.2, 3.7 Hz), 2.10 (td, 1H, J=12.6, 3.1 Hz), 1.89–1.85 (m, 1H), 1.63–1.38 (m, 3H); minor isomer δ 7.41–7.04 (m, 15H), 5.11–5.09 (m, 3H), 4.92–4.87 (m, 1H), 3.59 (ddd, 1H, J=13.6, 6.4, 4.0 Hz), 3.36–3.20 (m, 2H), 3.11–2.93 (m, 4H), 3.14, 2.87 (2ddd, 2H, J=13.4, 8.8, 3.7 Hz, partially overlapping with the next signal), 2.71–2.64 (m, 1H), 2.47–2.41 (m, 1H), 1.77–1.70 (m, 1H), 1.63–1.38 (m, 2H), 0.98–0.89 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.2, 172.9, 171.9, 171.9, 162.0, 161.9, 151.7, 151.6, 140.2, 135.7, 135.6, 135.5, 129.6, 129.5, 128.7, 128.6, 128.6, 128.5, 128.4, 128.4, 128.1, 127.2, 127.1, 126.3, 73.3, 66.5, 66.4, 57.6, 57.5, 43.3, 43.1, 41.1, 40.8, 40.4, 39.0, 36.9, 34.2, 34.2, 30.1, 27.5, 27.2, 26.8, 26.1; $[\alpha]_D^{25}=-25.2$ (c 1.16, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 1790, 1730, 1701, 1670, 1454, 1375, 1173, 718, 696 cm^{-1}; HRMS (EI): found M^+ 554.2410, $C_{33}H_{34}N_2O_6$ requires M^+ 554.2416. Anal. Calcd for $C_{33}H_{34}N_2O_6$: C, 71.46; H, 6.18; N, 5.05; found: C, 71.51; H, 6.40; N, 4.84.

4.3.4. Deuterium labeling study of the carboximide 10. Under Ar atmosphere, the solution of the carboximide **10** (146.5 mg, 0.264 mmol) in anhydrous THF (2.6 mL) was cooled to −78 °C (MeOH-dry ice bath), and LDA (1.8 M solution in heptane/THF/ethylbenzene, 0.18 mL, 0.32 mmol) was added dropwise. After stirring for 0.5 h at the same temperature, acetic acid-*d* (99at.% D) (0.31 mL, 5.28 mmol) was added slowly and the reaction mixture was stirred for 1 h at room temperature. The solution was poured into ice-cold satd NH_4Cl aq and the organic phase was extracted with AcOEt, washed with 5% $NaHCO_3$ aq, water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting oil was subjected to preparative TLC (*n*-hexane/AcOEt=3:2, 2 times development) to yield the products as a white powder (124.7 mg, 85%). The content of deuterium-incorporated **12** was detected by NMR. R_f=0.53 (*n*-hexane/AcOEt=1:1); mp 40–41 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.18 (m, 15H), 5.14, 5.10 (2d, 0.5×2H, J=12.3 Hz), 5.09 (s, 0.5×2H), 4.88 (d, 0.16H, J=4.6 Hz), 4.87 (d, 0.16H, J=4.4 Hz), 4.71–4.64 (m, 1H), 4.19 (dt, 0.5H, J=13.6, 4.2 Hz), 4.13 (dt, 0.5H, J=13.4, 4.2 Hz), 3.45–3.18 (m, 2.88H), 3.08–2.94 (m, 2H), 2.87–2.32 (m, 5H), 1.91–1.86 (m, 1H), 1.65–1.38 (m, 2H and 0.5H), 1.18–1.10 (m, 0.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 173.3, 172.1, 172.1, 164.8, 164.7, 152.5, 152.4, 140.3, 140.3, 135.7, 135.6, 135.2, 129.6, 129.5, 129.3, 129.3, 128.6, 128.6, 128.5, 128.4, 128.4, 128.2, 128.1, 128.1, 127.7, 126.2, 71.8, 71.6, 71.5 (t, J=24.1 Hz), 66.5, 66.5, 59.2, 59.1, 58.9, 58.8, 43.5, 43.3, 41.7, 41.6, 40.4, 40.3, 37.8, 37.7, 37.1, 37.0, 30.2, 28.2, 28.0, 27.4, 27.3; $[\alpha]_D^{26}=-15.1$ (c 1.55, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 1796, 1732, 1703, 1661, 1454, 1379, 1198, 1173, 772, 756, 727, 700, 679, 667 cm^{-1}; HRMS (EI): found M^+ 555.2478, $C_{33}H_{33}DN_2O_6$ requires M^+ 555.2479. Anal. Calcd for $C_{33}H_{33}DN_2O_6$: C, 71.33; H+D, 6.35; N, 5.04; found: C, 71.26; H+D, 6.06; N, 4.99.

4.4. Synthesis of *trans*-configured oxazolidinone 14 and *N*-3-phenylpropionylated carboximide 16

4.4.1. Benzyl *N*-[(4*S*,5*R*)-4-benzyl-1,3-oxazolidin-2-one-5-carbonyl]piperidine-4-carboxylate 14. To a solution of Boc-Pns-OH **13** (12.4 g, 42.0 mmol), benzyl piperidine-4-carboxylate·HCl **7** (12.9 g, 50.4 mmol) and HOBt·H_2O (7.7 g, 50.4 mmol) in DMF (210 mL) was added EDC·HCl (9.7 g, 50.4 mmol) in parts at 0 °C. After stirring for 0.5 h at the same temperature, Et_3N (7.0 mL, 50.4 mmol) was added dropwise, then the reaction mixture was stirred overnight at room temperature. The solution was diluted with AcOEt and washed consecutively with 5% citric acid aq, 5% $NaHCO_3$ aq, water (×2) and brine. After the organic layer was dried over Na_2SO_4, the solvent was removed under reduced pressure. The resulting white powder (20.0 g, 96%) was used for the next reaction without any purification. R_f=0.52 (*n*-hexane/AcOEt=1:1); mp 34–36 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.21 (m, 10H), 5.17, 5.12 (2d, 0.5×2H, J=12.5 Hz), 5.10 (s, 0.5×2H), 4.87 (br d, 0.5H, J=10.8 Hz), 4.71 (br d, 0.5H, J=10.3 Hz), 4.28–4.01 (m, 4H), 3.13–2.68 (m, 5H), 2.62–2.47 (m, 1H), 2.08–1.33 (m, 4H), 1.39 (s, 0.5×9H), 1.38 (s, 0.5×9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.6, 173.3, 170.3, 155.3, 155.2, 137.9, 137.7, 135.8, 135.6, 129.3, 128.6, 128.5, 128.2, 128.1, 128.0, 126.7, 79.4, 66.9, 66.6, 66.3, 53.8, 53.1, 43.7, 43.3, 42.1, 41.7, 41.0, 40.2, 38.8, 38.6, 28.2, 27.5, 27.2, 27.1, 26.7; $[\alpha]_D^{25}=-20.0$ (c 0.47, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 3439, 3005, 1717, 1701, 1639, 1499, 1454, 1393, 1367, 1240, 1169, 700 cm^{-1}; HRMS (EI): found M^+ 496.2568, $C_{28}H_{36}N_2O_6$ requires M^+ 496.2573. Anal. Calcd for $C_{28}H_{36}N_2O_6$: C, 67.72; H, 7.31; N, 5.64; found: C, 67.65; H, 7.31; N, 5.90.

Obtained dipeptide (20.0 g, 40.3 mmol) was treated with 4 M HCl/dioxane (140 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 2.5 h. After the solvent was removed under reduced pressure, the colorless oil obtained was dissolved in anhydrous THF (400 mL). To this solution was added Et_3N (8.4 mL, 60.5 mmol) dropwise at 0 °C, followed by the addition of CDI (9.8 g, 60.5 mmol). The cloudy reaction mixture was stirred overnight at room temperature, diluted with AcOEt, and washed consecutively with 5% citric acid aq, 5% $NaHCO_3$ aq, water and brine. After the organic layer was dried over Na_2SO_4, the solvent was removed under reduced pressure and the residue was applied to silica-gel column chromatography (*n*-hexane/AcOEt=1:2) to yield **14** as a white powder (15.0 g, 88% for 2 steps). R_f=0.55 (*n*-hexane/AcOEt=1:5); mp 91–93 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.20 (m, 10H), 5.28 (br s, 0.5H,), 5.25 (br s, 0.5H), 5.14 (s, 0.5×2H), 5.12 (s, 0.5×2H), 4.80 (d, 0.5H, J=5.3 Hz), 4.79 (d, 0.5H, J=5.1 Hz),

4.69–4.64 (m, 1H), 4.40–4.37 (m, 0.5H), 4.19 (dt, 0.5H, J= 13.6, 4.2 Hz), 3.89–3.86 (m, 0.5H), 3.74–3.71 (m, 0.5H), 3.23, 3.0 (2br t, 0.5×2H, J=11.2 Hz, partially overlapping with the next signal), 3.06–2.77 (m, 3H), 2.67–2.55 (m, 1H), 1.99–1.59 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.7, 173.4, 164.4, 164.3, 156.9, 135.8, 135.8, 135.7, 129.1, 129.0, 128.6, 128.3, 128.3, 128.1, 127.3, 76.8, 76.6, 66.5, 55.3, 44.8, 44.5, 42.0, 41.8, 41.0, 41.0, 40.9, 40.3, 28.4, 28.2, 27.5, 27.5; $[\alpha]_D^{27}=-91.2$ (c 1.28, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 3452, 3036, 3007, 1771, 1730, 1653, 1456, 1387, 1313, 1271, 1238, 1209, 1173, 1038, 1011, 756, 737, 698, 667 cm^{-1}; HRMS (EI): found M^+ 422.1845, $C_{24}H_{26}N_2O_5$ requires M^+ 422.1842. Anal. Calcd for $C_{24}H_{26}N_2O_5$: C, 68.23; H, 6.20; N, 6.63; found: C, 67.99; H, 6.20; N, 6.55.

4.4.2. *N*-{*N*-[(4*S*,5*R*)-4-benzyl-1,3-oxazolidin-2-one-5-carbonyl]piperidine-4-carboxyl}-(*R*)-1-phenethyl amide 15. To a solution of oxazolidinone **14** (141.1 mg, 0.334 mmol) in MeOH (3.0 mL) and water (0.35 mL) was added 5% Pd-C (15.2 mg), and the reaction mixture was stirred for 3 h under H_2 atomosphere. The reaction mixture was purged with Ar, then filtered through a pad of Celite® with MeOH. After evaporation, the resulting oil was diluted with AcOEt, and washed consecutively with water and brine. After the organic layer was dried over Na_2SO_4, the solvent was removed under reduced pressure. To a solution of this carboxylic acid in DMF (4.0 mL) was added $HOBt\cdot H_2O$ (61.3 mg, 0.401 mmol) and EDC·HCl (61.3 mg, 0.401 mmol) at 0 °C. After the mixture was stirred for 0.5 h at the same temperature, (*R*)-α-methylbenzylamine (51.6 μL, 0.401 mmol) was added dropwise. The reaction mixture was stirred for overnight at room temperature, then diluted with AcOEt and washed with 5% citric acid aq, 5% $NaHCO_3$ aq, water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the resulting crude product was purified by preparative TLC ($CHCl_3$/MeOH=10:1, 2 times development) to yield amide **15** as a white powder (133.7 mg, 92% for 2 steps). Recrystalization of the obtained white powder from $CHCl_3$ afforded the white needles, which was analyzed by X-ray crystallography. R_f=0.34 ($CHCl_3$/MeOH=10:1); mp 190–191 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.20 (m, 10H), 5.75 (br d, 0.5H, J= 8.1 Hz), 5.72 (br d, 0.5H, J=8.4 Hz), 5.13 (q, 0.5H, J= 6.8 Hz), 5.11 (q, 0.5H, J=7.0 Hz), 5.06 (s, 0.5H), 5.05 (s, 0.5H), 4.81 (d, 0.5H, J=5.5 Hz), 4.79 (d, 0.5H, J=5.7 Hz), 4.69–4.64 (m, 1H), 4.56–4.52 (m, 0.5H), 4.45–4.39 (m, 0.5H), 3.95–3.99 (m, 0.5H), 3.87–3.82 (m, 0.5H), 3.16, 2.87 (2ddd, 0.5×2H, J=14.3, 11.5, 2.9 Hz, partially overlapping with the next signal), 3.01–2.67 (m, 3H), 2.39–2.29 (m, 1H), 1.94–1.54 (m, 4H), 1.50 (d, 0.5×3H, J= 7.0 Hz), 1.48 (d, 0.5×3H, J=6.8 Hz); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 172.8, 165.6, 165.5, 157.4, 145.0, 144.8, 136.3, 136.2, 129.6, 129.5, 128.6, 128.3, 126.8, 126.6, 125.8, 74.3, 74.1, 55.8, 55.5, 47.6, 44.0, 41.4, 41.3, 28.9, 28.1, 27.7, 22.5; $[\alpha]_D^{25}=+9.4$ (c 1.05, MeOH); HRMS (EI): found M^+ 435.2157, $C_{25}H_{29}N_3O_4$ requires M^+ 435.2158.

4.4.3. Crystallography of amide 15. Diffraction data for **15** were collected on a Rigaku AFC7R diffractometer with graphite monochromated Cu Kα radiation (λ=1.54178 Å) and a rotating anode generator. All calculations were performed using the teXsan crystallographic software package of Molecular Structure Corporation. Formula $C_{25}H_{29}N_3O_4$, formula weight=435.52, orthorhombic, space group $P2_12_12_1$ (#19), a=17.986(2), b=23.841(2), c=5.269(3) Å, V=2259(1) Å^3, Z=4, D_{calc}=1.280 g/cm^3, F_{000}=928.00, μ(Cu Kα)=7.10 cm^{-1}. Total of 1554 unique reflections (complete for $2\theta<110°$) was used in the solution and refinement of structure. The structure was solved by direct methods using SAPI91,[45] and expanded using Fourier techniques with DIRDIF94 program.[46] The final refinement was done by the full-matrix least-squares method with anisotropic thermal parameters for all non-hydrogen atoms, and hydrogen atoms were included but not refined. The final R value was 0.238 (R_w=0.087).

4.4.4. Benzyl *N*-[(4*S*,5*R*)-4-benzyl-(3-phenylpropionyl)-1,3-oxazolidin-2-one-5-carbonyl]piperidine-4-carboxylate 16. To a solution of 3-phenylpropionic acid (6.8 g, 45.2 mmol) in anhydrous THF (100 mL) was added Et_3N (12.2 mL, 87.0 mmol) and trimethylacetylchloride (5.2 mL, 41.8 mmol) dropwise at -18 °C. The reaction mixture was stirred at the same temperature for 0.5 h, then anhydrous LiCl (1.6 g, 38.3 mmol) was added, followed by the slow addition of a solution of oxazolidinone **14** (14.7 g, 34.8 mmol) in anhydrous THF (75 mL). After the addition was completed, the reaction mixture was stirred overnight at room temperature. The solution was poured into ice-cold satd $NaHCO_3$ aq and the organic phase was extracted with AcOEt, washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting oil was applied to silica-gel column chromatography (*n*-hexane/AcOEt=4:1) to yield the desired compound **16** as a white solid (18.5 g, 96%). R_f= 0.52 (*n*-hexane/AcOEt=1:1); mp 39–41 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.18 (m, 15H), 5.14, 5.10 (2d, 0.5×2H, J=12.3 Hz), 5.09 (s, 0.5×2H), 4.88 (d, 0.5H, J= 4.4 Hz), 4.87 (d, 0.5H, J=4.4 Hz), 4.71–4.65 (m, 1H), 4.19 (dt, 0.5H, J=13.7, 4.0 Hz), 4.13 (dt, 0.5H, J=13.4, 4.2 Hz), 3.45–3.18 (m, 3H), 3.08–2.94 (m, 2H), 2.83–2.33 (m, 5H), 1.92–1.86 (m, 1H), 1.65–1.39 (m, 2H and 0.5H), 1.19–1.09 (m, 0.5H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.1, 171.9, 164.7, 164.5, 152.4, 152.3, 140.2, 135.6, 135.5, 135.0, 129.4, 129.3, 129.2, 129.1, 128.4, 128.3, 128.3, 128.2, 128.2, 127.9, 127.9, 127.5, 126.0, 71.7, 71.5, 66.3, 59.2, 58.8, 43.3, 43.1, 41.5, 41.4, 40.2, 40.1, 37.6, 37.5, 36.9, 36.9, 30.0, 28.0, 27.9, 27.2; $[\alpha]_D^{26}=-16.7$ (c 2.09, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 3040, 3007, 1794, 1728, 1701, 1659, 1497, 1454, 1379, 1310, 1292, 1263, 1244, 1171, 1103, 1078, 1030, 694 cm^{-1}; HRMS (EI): found M^+ 554.2410, $C_{33}H_{34}N_2O_6$ requires M^+ 554.2416. Anal. Calcd for $C_{33}H_{34}N_2O_6$: C, 71.46; H, 6.18; N, 5.05; found: C, 71.28; H, 5.99; N, 5.34.

4.4.5. Deuterium labeling study of the carboximide 16. Under Ar atmosphere, the solution of the carboximide **16** (142.4 mg, 0.257 mmol) in anhydrous THF (2.6 mL) was cooled to −78 °C (MeOH-dry ice bath), and LDA (1.8 M solution in heptane / THF / ethylbenzene, 0.17 mL, 0.31 mmol) was added dropwise. After stirring for 0.5 h at the same temperature, acetic acid-*d* (99at.% D) (0.30 mL, 5.14 mmol) was added slowly, then cooling bath was removed and the reaction mixture was stirred for 1 h at room

temperature. The solution was poured into ice-cold satd NH_4Cl aq and the organic phase was extracted with AcOEt, washed with 5% $NaHCO_3$ aq, water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting oil was subjected to preparative TLC (*n*-hexane/AcOEt=1:1) to yield the products as a white powder (125.7 mg, 88%). The content of deuterium-incorporated **17** was detected by NMR. R_f=0.53 (*n*-hexane/AcOEt=1:1); mp 39–40 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.18 (m, 15H), 5.14, 5.10 (2d, 0.5×2H, J=12.3 Hz), 5.09 (s, 0.5×2H), 4.88 (d, 0.5H, J=4.6 Hz), 4.87 (d, 0.5H, J=4.6 Hz), 4.71–4.64 (m, 1H), 4.19 (dt, 0.5H, J=13.6, 4.0 Hz), 4.13 (dt, 0.5H, J=13.2, 4.0 Hz), 3.44–3.18 (m, 2.24H), 3.06–2.94 (m, 2H), 2.83–2.33 (m, 5H), 1.91–1.86 (m, 1H), 1.64–1.38 (m, 2H and 0.5H), 1.18–1.08 (m, 0.5H); ^{2}H NMR (400 MHz, $CHCl_3$) δ 3.32 (s, 0.76D); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.3, 172.1, 164.8, 164.6, 152.5, 152.4, 140.3, 135.7, 135.6, 135.2, 129.5, 129.5, 129.3, 129.3, 128.6, 128.5, 128.4, 128.4, 128.1, 127.7, 126.2, 71.8, 71.6, 66.5, 59.2, 58.9, 43.5, 43.3, 41.7, 41.6, 40.3, 37.8, 37.7, 37.1, 37.0, 36.7 (t, J=19.9 Hz), 30.1, 30.1, 28.2, 28.0, 27.3; $[\alpha]_D^{27}=-14.8$ (*c* 1.69, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 1792, 1732, 1703, 1661, 1454, 1371, 1236, 1196, 1186, 1173, 797, 725, 700, 673 cm^{-1}; HRMS (EI): found M^+ 555.2482, $C_{33}H_{33}DN_2O_6$ requires M^+ 555.2479. Anal. Calcd for $C_{33}H_{33}DN_2O_6$: C, 71.33; H+D, 6.35; N, 5.04; found: C, 71.17; H+D, 6.29; N, 5.01.

4.5. Preparation of the Wang resin-supported oxazolidinone 23 by Fmoc-based solid-phase synthesis

Wang resin (0.80 mmol/g resin) (5.0 g, 4.0 mmol) in a cap-fitted reaction vessel was washed with CH_2Cl_2 (20 mL, ×5), then Fmoc-piperidine-4-carboxylic acid **20** (4.2 g, 12.0 mmol) and CH_2Cl_2 (30 mL) were charged. DIPCDI (1.9 mL, 12.0 mmol) was added, followed by the addition of DMAP (48.7 mg, 0.4 mmol). The heterogeneous reaction mixture was vigorously shaken for 2 h at room temperature, then filtered and washed with DMF (20 mL, ×5). The obtained white resin **21** was then washed with piperidine in DMF (20%, v/v) (20 mL, ×5) and treated with piperidine in DMF (20%, v/v) (30 mL) for 0.5 h at room temperature. The solvent and reagent were drained and the resin was washed with DMF (20 mL), $CHCl_3$ (20 mL), DMF (20 mL) (×5, sequentially). Next, Fmoc-Pns-OH (5.0 g, 12.0 mmol), HOBt·H_2O (1.8 g, 12.0 mmol), DMF (30 mL) and DIPCDI (1.9 mL, 12.0 mmol) were added, and the heterogenious reaction mixture was vigorously shaken for 2 h at room temperature, then filtered and washed with DMF (20 mL, ×5). The aliquot of the resultant resin **22** was applied to the Kaiser-Test[47] to check the reaction progress. Starting secondary amine resin was positive (pale orange), whereas the dipeptide-bound resin **22** was negative (colorless). The obtained resin **22** was washed with piperidine in DMF (20%, v/v) (20 mL, ×5) and treated with piperidine in DMF (20%, v/v) (30 mL) for 0.5 h at room temperature. The solvent and reagent were drained and the resin was washed with DMF (20 mL), $CHCl_3$ (20 mL), DMF (20 mL) (×5, sequentially). The obtained amino alcohol resin was washed with THF (20 mL, ×5), then CDI (1.9 g, 12.0 mmol) and anhydrous THF (30 mL) were added. The heterogenious reaction mixture was vigorously shaken for 3 h at room temperature, then filtered and washed with THF (20 mL, ×5). Kaiser-Test of the starting primary amine resin was positive (blue), whereas the oxazolidinone resin **23** was negative (colorless). The obtained resin was washed with $CHCl_3$ (20 mL) and MeOH (20 mL) (×5, sequentially), then overnight drying in vacuo afforded the desired pale yellowish oxazolidinone resin **23** (6.3 g) with loading rate of 0.61 mmol/g.

4.5.1. *O*-Wang resin-supported *N*-[(9*H*-9-fluorenylmethoxy)carbonyl]piperidine-4-carboxylic acid 21. FT-IR (KBr) ν_{max} 1736, 1719 cm^{-1}.

4.5.2. *O*-Wang resin-supported *N*-((2*R*,3*S*)-3-{[(9*H*-9-fluorenylmethoxy)carbonyl]amino}-2-hydroxy-4-phenylbutanoyl)piperidine-4-carboxylic acid 22. FT-IR (KBr) ν_{max} 3398, 1733, 1718, 1638 cm^{-1}.

4.5.3. *O*-Wang resin-supported *N*-[(4*S*,5*R*)-4-benzyl-1,3-oxazolidin-2-one-3-carbonyl]piperidine-4-carboxylic acid 23. FT-IR (KBr) ν_{max} 1763, 1740, 1655 cm^{-1}.

4.5.4. Methanolysis of the oxazolidinone resin 23 to afford the methyl *N*-[(4*S*,5*R*)-4-benzyl-1,3-oxazolidin-2-one-5-carbonyl]piperidine-4-carboxylate 24. Oxazolidinone-loaded resin **23** (129.9 mg, 0.083 mmol) was swollen in anhydrous THF (0.85 mL) and anhydrous MeOH (0.85 mL), then potassium carbonate (22.9 mg, 0.166 mmol) was added in one portion at 0 °C. The heterogeneous reaction mixture was gently stirred for 2 h at room temperature. The reaction was quenched by the addition of satd NH_4Cl aq, and the resultant resin was removed by filtration. The filtrate was extracted with AcOEt, and washed with water and brine, then dried over Na_2SO_4. After solvent removal, the remaining crude oil was purified by preparative TLC (*n*-hexane/AcOEt=1:10) to yield the oxazolidinone methyl ester **24** as a white solid (27.4 mg, 95% in 6 steps from Wang resin). R_f=0.30 (*n*-hexane/AcOEt=1:5); mp 39–40 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.21 (m, 5H), 5.73 (br s, 1H), 4.82 (d, 0.5H, J=5.5 Hz), 4.80 (d, 0.5H, J=5.5 Hz), 4.67–4.62 (m, 1H), 4.39–4.34 (m, 0.5H), 4.19 (dt, 0.5H, J=13.6, 4.0 Hz), 3.83–3.79 (m, 0.5H), 3.70–3.65 (m, 0.5H, partially overlapping with the next signal), 3.70 (s, 0.5×3H), 3.68 (s, 0.5×3H), 3.20, 3.00 (2ddd, 0.5×2H, J=14.1, 10.6, 3.1 Hz, partially overlapping with the next signal), 2.99–2.78 (m, 3H), 2.61–2.50 (m, 1H), 1.96–1.54 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 174.3, 174.1, 164.5, 164.4, 157.1, 135.8, 135.7, 129.1, 128.8, 127.1, 76.4, 76.3, 55.4, 55.3, 51.8, 44.7, 44.4, 41.9, 41.7, 40.8, 40.7, 40.6, 40.1, 28.3, 28.1, 27.4; $[\alpha]_D^{25}=-104.4$ (*c* 0.55, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 3454, 3007, 2955, 1771, 1732, 1655, 1456, 1437, 1383, 1317, 1269, 1240, 1194, 1177, 1040, 1015, 760, 745 cm^{-1}; HRMS (EI): found M^+ 346.1526, $C_{18}H_{22}N_2O_5$ requires M^+ 346.1528. Anal. Calcd for $C_{18}H_{22}N_2O_5\cdot0.25H_2O$: C, 61.61; H, 6.46; N, 7.98; found: C, 61.99; H, 6.26; N, 7.96.

4.6. General procedure for *N*-acylation of the Wang resin-supported oxazolidinone resin 23, solid-phase asymmetric alkylation, lithium hydroperoxide-mediated hydrolysis, and the derivatization to the (*S*)-phenylethylamide for enantiomeric excess determination

Oxazolidinone-loaded resin **23** in a polystyrene reactor was washed with CH_2Cl_2 (×5), then the corresponding

carboxylic acid (3.0 equiv), 2-chloro-1-methylpyridinium iodide (3.0 equiv) and anhydrous CH_2Cl_2 (0.08 mmol resin/mL) were added. The mixture was shaken for 10 min, followed by the addition of Et_3N (5.0 equiv) and DMAP (0.3 equiv). The reaction mixture was shaken for 2 h at room temperature and filtered, then the resultant resin was washed with CH_2Cl_2 (×5). The reaction was repeated once again, and the obtained resin was washed with DMF, $CHCl_3$ and MeOH (×5, sequentially), then overnight drying in vacuo afforded the desired carboximide resin **25**. Under Ar atmosphere, carboximide resin **25** in a glass reaction vessel was swollen in THF (20 mL/mmol resin) for 10 min at room temperature, and the heterogeneous mixture was cooled to −78 °C (MeOH-dry ice bath), followed by the dropwise addition of 1.0 M THF solution of NaHMDS (3.0 equiv). After continuously stirring for 1 h at the same temperature, the corresponding alkyl halide (10.0 equiv) was added. The temperature of the reaction mixture was gradually increased up to 0 °C over 12 h with gentle stirring, then quenched by the addition of satd NH_4Cl aq, and tri-phase reaction mixture was stirred for additional 15 min. at 0 °C. The resultant resin was separated from the reaction mixture by filtration, followed by washing with THF-H_2O (1:1), THF and MeOH (×5, sequentially). Then, the resin was dried well in the desiccator under reduced pressure for 3 h. THF-H_2O (3:1, v/v) (0.05 mmol resin/mL) was added to the α-alkylated carboximide resin, and the resin was swollen for 10 min. at 0 °C. Next, 30% aqueous H_2O_2 (6.0 equiv) and $LiOH\cdot H_2O$ (3.0 equiv) were added. After gentle stirring for 2 h at the same temperature, the reaction was quenched by the addition of 1.5 N $NaHSO_3$ aq, and the deacylated resin was filtered off. The filtrate was acidified to pH 2 with 1 N HCl aq, and extracted with AcOEt. The extract was washed with brine, and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by preparative TLC to yield the desired α-alkylated carboxylic acids **26**. The recovered oxazolidinone resin **23** was washed with THF, $CHCl_3$ and MeOH (×5, sequentially), then dried in the desiccator under reduced pressure. Determination of the enantiomeric excess of the obtained carboxylic acids **26** was carried out by derivatization to the corresponding (*S*)-phenylethyl amides and chiral HPLC analysis. To a 0.05 M solution of the acids **26** in DMF was added $HOBt\cdot H_2O$ (1.2 equiv) and EDC·HCl (1.2 equiv) at 0 °C. The mixture was stirred for 0.5 h at the same temperature, and (*S*)-phenylethylamine (1.2 equiv) was added dropwise. The reaction mixture was stirred overnight at room temperature, then diluted with AcOEt and washed with 5% citric acid aq, 5% $NaHCO_3$ aq, water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the resulting amide was subjected to the HPLC analysis without any purification. Enantiomeric excess was calculated from the peak areas of the corresponding two diastereomers.

4.6.1. (*S*)-2-Benzylpropanoic acid 26a. The title compound **26a** was obtained according to the general procedure using the oxazolidinone resin **23** (277.5 mg, 0.169 mmol). Purification by preparative TLC (*n*-hexane/AcOEt=1:1) gave **26a** as a colorless oil (16.8 mg, 61% yield in 3 steps from oxazolidinone resin **23**). R_f=0.63 (*n*-hexane/AcOEt=1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.17 (m, 5H), 3.08 (dd, 1H, J=13.0, 6.1 Hz), 2.83–2.71 (m, 1H), 2.67 (dd, 1H, J=13.0, 7.9 Hz), 1.18 (d, 3H, J=6.8 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 181.7, 139.0, 129.0, 128.4, 126.4, 41.1, 39.3, 16.5; $[\alpha]_D^{28}$=+20.6 (*c* 0.87, $CHCl_3$): lit.,[48] $[\alpha]_D$=+25.5 (*c* 1.00, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 3038, 2980, 1709, 1454, 1238, 719, 698, 675 cm^{-1}; HRMS (EI): found M^+ 164.0838, $C_{10}H_{12}O_2$ requires M^+ 164.0837. Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37; found: C, 73.25; H, 7.47. Enantiomeric excess was 85% ee determined by chiral HPLC analysis of the corresponding (*S*)-α-methylbenzylamine-derived amide with Chiralcel® OD normal phase column (*n*-hexane/EtOH=30/1, 1.0 mL/min, 230 nm), major isomer=13.1 min, minor isomer=16.8 min.

4.6.2. (*S*)-2-Benzylbutanoic acid 26b. The title compound **26b** was obtained according to the general procedure using the oxazolidinone resin **23** (193.8 mg, 0.118 mmol). Purification by preparative TLC ($CHCl_3$/MeOH=10:1) gave **26b** as a colorless oil (10.6 mg, 50% yield in 3 steps from oxazolidinone resin **23**). R_f=0.53 ($CHCl_3$/MeOH=10:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.16 (m, 5H), 2.98 (dd, 1H, J=13.6, 7.7 Hz), 2.75 (dd, 1H, J=13.6, 6.8 Hz), 2.66–2.57 (m, 1H), 1.72–1.54 (m, 2H), 0.96 (t, 3H, J=7.3 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 181.3, 139.1, 128.9, 128.4, 126.4, 48.8, 37.7, 24.7, 11.6; $[\alpha]_D^{26}$=+30.7 (*c* 0.86, benzene): lit.,[49] $[\alpha]_D^{24}$=+34.7 (*c* 8.45, benzene); FT-IR ($CHCl_3$) ν_{max} 1707, 1462, 1383, 1096, 899, 696, 652 cm^{-1}; HRMS (EI): found M^+ 178.0999, $C_{11}H_{14}O_2$ requires M^+ 178.0994. Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92; found: C, 73.99; H, 7.99. Enantiomeric excess was 88% ee determined by chiral HPLC analysis of the corresponding (*S*)-α-methylbenzylamine-derived amide with Chiralcel® OD normal phase column (*n*-hexane/EtOH=30/1, 1.0 mL/min, 230 nm), major isomer=11.3 min, minor isomer=16.1 min.

4.6.3. (*S*)-2-Benzyl-4-pentenoic acid 26c. The title compound **26c** was obtained according to the general procedure using the oxazolidinone resin **23** (302.1 mg, 0.184 mmol). Purification by preparative TLC ($CHCl_3$/MeOH=10:1) gave **26c** as a colorless oil (23.8 mg, 68% yield in 3 steps from oxazolidinone resin **23**). R_f=0.50 ($CHCl_3$/MeOH=10:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.16 (m, 5H), 5.78 (ddt, 1H, J=17.1, 10.3,7.0 Hz), 5.12–5.05 (m, 2H), 3.03–2.94 (m, 1H), 2.82–2.72 (m, 2H), 2.44–2.25 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 180.7, 138.8, 134.7, 128.9, 128.5, 126.5, 117.5, 46.9, 37.3, 35.6; $[\alpha]_D^{26}$=+24.0 (*c* 1.27, $CHCl_3$): lit.,[33] $[\alpha]_D^{25}$=+19.2 (*c* 12.2, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 3084, 3067, 3038, 1709, 922, 802, 775, 764, 746, 739, 729, 721, 700, 675, 667 cm^{-1}; HRMS (EI): found M^+ 190.0989, $C_{12}H_{14}O_2$ requires M^+ 190.0994. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42; found: C, 75.50; H, 7.50. Enantiomeric excess was 96% ee determined by chiral HPLC analysis of the corresponding (*S*)-α-methylbenzylamine-derived amide with Chiralcel® OD normal phase column (*n*-hexane/EtOH=30/1, 1.0 mL/min, 230 nm), major isomer=11.6 min, minor isomer=15.2 min.

4.6.4. (*S*)-2-Benzyl-4-pentynoic acid 26d. The title compound **26d** was obtained according to the general procedure using the oxazolidinone resin **23** (206.9 mg, 0.126 mmol). Purification by preparative TLC ($CHCl_3$/MeOH=10:1) gave **26d** as a colorless oil (14.7 mg, 62% yield in 3 steps from oxazolidinone resin **23**). R_f=0.44 ($CHCl_3$/MeOH=10:1); ^{1}H

NMR (300 MHz, $CDCl_3$) δ 7.31–7.20 (m, 5H), 3.09 (dd, 1H, J=13.4, 6.6 Hz), 2.99–2.85 (m, 2H), 2.44 (dd, 2H, J=6.4, 2.6 Hz), 2.06 (t, 1H, J=2.6 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 179.5, 138.1, 129.0, 128.5, 126.7, 80.9, 70.6, 45.9, 36.3, 20.0; $[\alpha]_D^{26}=-10.9$ (c 1.24, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 3308, 1719, 1217, 1200, 770, 700, 671 cm^{-1}; HRMS (EI): found M^+ 188.0835, $C_{12}H_{12}O_2$ requires M^+ 188.0837. Anal. Calcd for $C_{12}H_{12}O_2\cdot 0.25H_2O$: C, 74.78; H, 6.54; found: C, 75.14; H, 6.57. Enantiomeric excess was 96% ee determined by chiral HPLC analysis of the corresponding (*S*)-α-methylbenzylamine-derived amide with Chiralcel® OD normal phase column (*n*-hexane/EtOH=30/1, 1.0 mL/min, 230 nm), major isomer=16.4 min, minor isomer=18.6 min.

4.6.5. (*R*)-2-Benzyl-4-ethoxy-4-oxobutanoic acid 26e. The title compound **26e** was obtained according to the general procedure using the oxazolidinone resin **23** (259.8 mg, 0.158 mmol). Purification by preparative TLC ($CHCl_3$/MeOH=10:1) gave **26e** as a colorless oil (23.1 mg, 62% yield in 3 steps from oxazolidinone resin **23**). R_f=0.41 ($CHCl_3$/MeOH=10:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.17 (m, 5H), 4.11 (q, 2H, J=7.2 Hz), 3.21–3.10 (m, 2H), 2.83–2.74 (m, 1H), 2.64 (dd, 1H, J=17.0, 8.9 Hz), 2.41 (dd, 1H, J=17.0, 4.6 Hz), 1.22 (t, 3H, J=7.2 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 179.5, 171.7, 137.9, 129.1, 128.6, 126.8, 60.8, 42.8, 37.4, 34.8, 14.1; $[\alpha]_D^{26}=+10.6$ (c 1.15, $CHCl_3$): lit.,[50] $[\alpha]_D^{28}=+10.0$ (c 2.9, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 1732, 1717, 910, 777, 754, 739, 721, 700, 679, 652 cm^{-1}; HRMS (EI): found M^+ 236.1051, $C_{13}H_{16}O_4$ requires M^+ 236.1048. Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83; found: C, 65.93; H, 6.81. Enantiomeric excess was 92% ee determined by chiral HPLC analysis of the corresponding (*S*)-α-methylbenzylamine-derived amide with Chiralcel® OD normal phase column (*n*-hexane/EtOH=30/1, 1.0 mL/min, 230 nm), major isomer=15.7 min, minor isomer=16.6 min.

4.6.6. (*R*)-2-Benzylpropanoic acid 26f. The title compound **26f** was obtained according to the general procedure using the oxazolidinone resin **23** (236.5 mg, 0.144 mmol). Purification by preparative TLC (*n*-hexane/AcOEt=1:1) gave **26f** as a colorless oil (16.6 mg, 70% yield in 3 steps from oxazolidinone resin **23**). R_f=0.63 (*n*-hexane/AcOEt=1:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.17 (m, 5H), 3.08 (dd, 1H, J=13.0, 6.1 Hz), 2.80–2.70 (m, 1H), 2.67 (dd. 1H, J=13.0, 7.9 Hz), 1.18 (d, 3H, J=6.8 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 182.3, 139.0, 129.0, 128.4, 126.4, 41.2, 39.3, 16.5; $[\alpha]_D^{28}=-30.7$ (c 1.04, $CHCl_3$): lit.,[51] $[\alpha]_D^{22}=-30.1$ (c 1.00, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 1707, 1464, 1381, 1231, 893, 800, 694, 648 cm^{-1}; HRMS (EI): found M^+ 164.0830, $C_{10}H_{12}O_2$ requires M^+ 164.0837. Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37; found: C, 72.94; H, 7.31. Enantiomeric excess was 97% ee determined by chiral HPLC analysis of the corresponding (*S*)-α-methylbenzylamine-derived amide with Chiralcel® OD normal phase column (*n*-hexane/EtOH=30/1, 1.0 mL/min, 230 nm), major isomer=16.8 min, minor isomer=13.1 min.

4.6.7. (*R*)-3-(4-Bromophenyl)-2-methylpropanoic acid 26g. The title compound **26g** was obtained according to the general procedure using the oxazolidinone resin **23** (185.5 mg, 0.113 mmol). Purification by preparative TLC ($CHCl_3$/MeOH=10:1) gave **26g** as a white powder (18.6 mg, 68% yield in 3 steps from oxazolidinone resin **23**). R_f=0.55 ($CHCl_3$/MeOH=10:1); mp 60–62 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, 2H, J=8.4 Hz), 7.06 (d, 2H, J=8.4 Hz), 3.01 (dd, 1H, J=13.0, 6.4 Hz), 2.77–2.68 (m, 1H), 2.64 (dd, 1H, J=13.0, 7.5 Hz), 1.18 (d, 3H, J=6.8 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 181.1, 138.0, 131.5, 130.7, 120.3, 40.9, 38.7, 16.6; $[\alpha]_D^{26}=-26.4$ (c 1.02, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 3030, 1711, 1466, 1381, 1231, 1215, 1097, 893, 800, 787, 750, 733, 725, 696, 677, 654 cm^{-1}; HRMS (EI): found M^+ 241.9949, $C_{10}H_{11}BrO_2$ requires M^+ 241.9942. Anal. Calcd for $C_{10}H_{11}BrO_2$: C, 49.41; H, 4.56; found: C, 49.56; H, 4.66. Enantiomeric excess was 97% ee determined by chiral HPLC analysis of the corresponding (*S*)-α-methylbenzylamine-derived amide with Chiralcel® OD normal phase column (*n*-hexane/EtOH=50/1, 1.0 mL/min, 230 nm), major isomer=30.8 min, minor isomer=27.5 min.

4.6.8. (*R*)-3-(4-Nitrophenyl)-2-methylpropanoic acid 26h. The title compound **26h** was obtained according to the general procedure using the oxazolidinone resin **23** (256.2 mg, 0.156 mmol). Purification by preparative TLC ($CHCl_3$/MeOH=10:1) gave **26h** as a pale yellowish powder (21.2 mg, 65% yield in 3 steps from oxazolidinone resin **23**). R_f=0.44 ($CHCl_3$/MeOH=10:1); mp 101–103 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, 2H, J=8.8 Hz), 7.36 (d, 2H, J=8.8 Hz), 3.15 (dd, 1H, J=16.5, 9.9 Hz), 2.86–2.77 (m, 2H), 1.23 (d, 3H, J=6.6 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 181.0, 146.9, 146.7, 129.8, 123.7, 40.8, 39.0, 16.8; $[\alpha]_D^{25}=-36.9$ (c 1.14, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 1713, 1607, 1522, 1464, 1381, 1348, 1231, 1097, 895, 733, 694, 648 cm^{-1}; HRMS (EI): found M^+ 209.0683, $C_{10}H_{11}NO_4$ requires M^+ for 209.0688. Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.70; found: C, 57.58; H, 5.39; N, 6.72. Enantiomeric excess was 97% ee determined by chiral HPLC analysis of the corresponding (*S*)-α-methylbenzylamine-derived amide with Chiralcel® OD normal phase column (*n*-hexane/EtOH=20/1, 1.0 mL/min, 230 nm), major isomer=33.2 min, minor isomer=37.5 min.

4.6.9. (*R*)-3-(2,4-Dichlorophenyl)-2-methylpropanoic acid 26i. The title compound **26i** was obtained according to the general procedure using the oxazolidinone resin **23** (251.2 mg, 0.153 mmol). Purification by preparative TLC ($CHCl_3$/MeOH=10:1) gave **26i** as a pale yellowish oil (25.3 mg, 71% yield in 3 steps from oxazolidinone resin **23**). R_f=0.56 ($CHCl_3$/MeOH=10:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (m, 1H), 7.16–7.15 (m, 2H), 3.12 (dd, 1H, J=12.8, 6.6 Hz), 2.90–2.82 (m, 1H), 2.79 (dd, 1H, J=12.8, 7.2 Hz), 1.22 (d, 3H, J=6.8 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 181.9, 135.4, 134.9, 133.0, 132.0, 129.4, 127.0, 39.3, 36.3, 16.8; $[\alpha]_D^{27}=-44.9$ (c 1.00, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 1709, 1474, 1383, 1103, 901, 870, 802, 725, 712, 677, 652 cm^{-1}; HRMS (EI): found M^+ 232.0055, $C_{10}H_{10}Cl_2O_2$ requires M^+ 232.0058. Anal. Calcd for $C_{10}H_{10}Cl_2O_2$: C, 51.53; H, 4.32; found: C, 51.68; H, 4.44. Enantiomeric excess was 97% ee determined by chiral HPLC analysis of the corresponding (*S*)-α-methylbenzylamine-derived amide with Chiralcel® OD normal phase column (*n*-hexane/EtOH=70/1, 1.0 mL/min, 230 nm), major isomer=24.2 min, minor isomer=21.7 min.

4.6.10. (*R*)-2-Phenoxy-4-pentenoic acid 26j. The title compound **26j** was obtained according to the general procedure using the oxazolidinone resin **23** (284.0 mg, 0.173 mmol). Purification by preparative TLC ($CHCl_3$/MeOH=10:1) gave **26j** as a white solid (16.7 mg, 50% yield in 3 steps from oxazolidinone resin **23**). R_f=0.48 ($CHCl_3$/MeOH=10:1); mp 30–31 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (br s, 1H), 7.31–7.25 (m, 2H), 7.02–6.98 (m, 1H), 6.90 (dd, 2H, J=8.8, 1.1 Hz), 5.91 (ddt, 1H, J=17.0, 10.3, 7.0 Hz), 5.21 (dd, 1H, J=17.0, 1.6 Hz), 5.16 (dd, 1H, J=10.3, 1.6 Hz), 4.72 (t, 1H, J=6.2 Hz), 2.72–2.76 (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$)? δ 176.5, 157.4, 131.9, 129.6, 122.1, 119.0, 115.3, 75.9, 36.8; $[\alpha]_D^{28}$=+7.9 (*c* 1.96, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 1732, 1599, 1495, 1238, 771, 750, 735, 691 cm^{-1}; HRMS (EI): found M^+ 192.0782, $C_{11}H_{12}O_3$ requires M^+ 192.0786. Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29; found: C, 68.49; H, 6.34. Enantiomeric excess was 96% ee determined by chiral HPLC analysis of the corresponding (*S*)-α-methylbenzylamine-derived amide with Chiralcel® OD normal phase column (*n*-hexane/EtOH=50/1, 1.0 mL/min, 230 nm), major isomer=8.3 min, minor isomer=9.8 min.

4.6.11. (*S*)-3-(2,4-Dichlorophenyl)-2-methylpropanoic acid 26k. The title compound **26k** was obtained according to the general procedure using the oxazolidinone resin **23** (208.5 mg, 0.127 mmol). Purification by preparative TLC ($CHCl_3$/MeOH=10:1) gave **26k** as a colorless oil (17.4 mg, 59% yield in 3 steps from oxazolidinone resin **23**). R_f=0.52 ($CHCl_3$/MeOH=10:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (m, 1H), 7.17–7.16 (m, 2H), 3.12 (dd, 1H, J=12.8, 6.6 Hz), 2.90–2.80 (m, 1H), 2.79 (dd, 1H, J=12.8, 7.3 Hz), 1.22 (d, 3H, J=6.8 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 181.8, 135.4, 134.9, 133.0, 132.1, 129.4, 127.0, 39.2, 36.3, 16.8; $[\alpha]_D^{27}$=+34.7 (*c* 0.95, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 1711, 1474, 901, 733, 698, 675, 667, 652 cm^{-1}; HRMS (EI): found M^+ 232.0054, $C_{10}H_{10}Cl_2O_2$ requires M^+ 232.0058. Anal. Calcd for $C_{10}H_{10}Cl_2O_2$: C, 51.53; H, 4.32; found: C, 51.93; H, 4.62. Enantiomeric excess was 85% ee determined by chiral HPLC analysis of the corresponding (*S*)-α-methylbenzylamine-derived amide with Chiralcel® OD normal phase column (*n*-hexane/EtOH=70/1, 1.0 mL/min, 230 nm), major isomer=21.7 min, minor isomer=24.2 min.

4.6.12. Reuse of the oxazolidinone resin 23 in solid-phase Evans' asymmetric allylation, and methanolysis of the oxazolidinone resin recovered after three-times recycling. Starting from the oxazolidinone resin **23** (298.9 mg, 0.182 mmol), reaction sequence (*N*-acylation with 3-phenylpropionic acid, asymmetric allylation, and LiOOH-mediated hydrolysis) was repeated three times according to the procedure for synthesizing carboxylic acid **26c**. Then, oxazolidinone-loaded resin **23** recovered after three-times recycling was subjected to the methanolysis condition following the same procedure for synthesizing ester **24**. After the reaction, the resultant crude oil was purified by preparative TLC (*n*-hexane/AcOEt=1:5) to yield the methyl ester **24** (45.3 mg, 72% calculated from the loading rate of the starting oxazolidinone resin **23**) and *N*-allylated oxazolidinone methyl ester **27** as a pale yellowish viscous oil (16.1 mg, 23% calculated by the loading rate of the starting oxazolidinone resin **23**). R_f=0.47 (*n*-hexane/AcOEt=1:5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.17 (m, 5H), 5.78 (dddd, 1H, J=17.2, 10.3, 7.3, 4.8 Hz), 5.26–5.19 (m, 2H), 4.70 (d, 0.5H, J=4.4 Hz), 4.69 (d, 0.5H, J=4.6 Hz), 4.66–4.60 (m, 1H), 4.30 (dtd, 0.5H, J=3.4, 4.0, 1.5 Hz), 4.24–4.21 (m, 0.5H), 4.20–4.17 (m, 0.5H), 4.15–4.10 (m, 0.5H), 3.68–3.51 (m, 2H), 3.69 (s, 0.5×3H), 3.67 (s, 0.5×3H, partially overlapping with the next signal), 3.15–2.71 (m, 4H), 2.56–2.45 (m, 1H), 1.91–1.38 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 174.3, 174.0, 164.5, 164.4, 156.0, 155.9, 135.3, 135.2, 131.6, 129.2, 128.9, 128.9, 127.3, 127.2, 118.9, 118.8, 73.5, 73.3, 57.0, 56.9, 51.8, 45.2, 44.7, 44.4, 41.9, 41.7, 40.7, 40.2, 38.1, 37.9, 28.4, 28.1, 27.5, 27.4; $[\alpha]_D^{26}$=−85.9 (*c* 1.19, $CHCl_3$); FT-IR ($CHCl_3$) ν_{max} 1753, 1746, 1655, 1456, 1437, 1175, 895, 648 cm^{-1}; HRMS (EI): found M^+ 386.1846, $C_{21}H_{26}N_2O_5$ requires M^+ 386.1841. Anal. Calcd for $C_{21}H_{26}N_2O_5$: C, 65.27; H, 6.78; N, 7.25; found: C, 64.99; H, 6.49; N, 7.47.

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31. Crystallographic data (excluding structural factors) for the structure **15** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 259416. Copies of the data can be obtained, free of charge, on application to CDCC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
32. The quenching study of lithium enolate generated from a similar derivative, *N*-propionylated carboximide, with TBSOTf, afforded the *O*-silyl enol ether as a single isomer in 82% yield. The irradiation to its olefinic methyl group gave a clear NOE enhancement for *tert*-butyldimethyl moiety (400 MHz, ^{1}H NMR, $CDCl_3$), suggesting that the reaction proceeded via a *Z*-configured lithium enolate intermediate.
33. The absolute stereochemistry of **26c** was determined in comparison of its $[\alpha]_D$ value with the reported authentic data in Kurth, M. J.; Decker, O. H. W.; Hope, H.; Yanuck, M. D. *J. Am. Chem. Soc.* **1985**, *107*, 443–448. Enantiomeric excess of **26c** was determined by HPLC analysis after conversion to the corresponding (*S*)-phenethylamide. Vedejs, E.; Gingras, M. *J. Am. Chem. Soc.* **1994**, *116*, 579–588.
34. Energy minimization was performed by systematic conformation search on the MMFF94x force field using the Molecular Operating Environment modeling package (MOE 2004.03, Chemical Computing Group, Inc., Montreal, Canada), followed by MOPAC (PM3 program).
35. This effect may be similar to the shielding effect observed in 5,5-dimethyl-4-benzyloxazolidinone, so-called 'SuperQuats'. Davies, S. G.; Sanganee, H. J.; Szolcsanyi, P. *Tetrahedron* **1999**, *55*, 3337–3354.
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38. Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 707–721. Insufficient introduction ($\sim$60%) of the *N*-3-phenylpropionyl group was observed in single coupling. Hence, double coupling was employed.
39. Other bases such as LiHMDS and KHMDS were less effective, and lower conversion was observed in the reaction below -20 °C.
40. (a) Preliminary stability test of **23** against LiOOH treatment revealed that ester linkage is sufficiently inert under the basic condition up to 8 h at 0 °C, and oxazolidinone ring was also stable enough. Kaiser-Test[47] of the recovered resin was completely negative, indicating that there is no free amino group caused by the oxazolidinone ring opening. Indeed, hydrolysis of the ester moiety was observed only in the H_2O_2 free condition. (b) Methanolysis of the recovered oxazolidinone resin **23** afforded the corresponding methyl ester **24** in 94% without any epimerization. Additionally there is no contamination of endo-cleavage byproduct as well as in the case of solution-phase model experiment.

41. 3-(2,4-Dichlorophenyl)propionic acid was prepared from *trans*-2,4-dichlorocinnamic acid in the following three-step reaction sequence (3 steps, 87%): (a) K_2CO_3, MeI, DMF, rt; (b) $NaBH_4$, CuCl, THF, 0 °C; (c) 1 N NaOH aq, MeOH, 50 °C. Unfortunately, simple hydrogenolysis of *trans*-2,4-dichlorocinnamic acid by H_2, 10% Pd–C in EtOH resulted in not only reduction of olefin moiety, but also de-chlorination at the 2-position on the aromatic ring. 2,4-Dichlorobenzyl iodide was prepared by iodination of the corresponding alcohol with NaI/Amberlyst. Tajbakhsh, M.; Hosseinzadeh, R.; Lasemi, Z. *Synlett* **2004**, *4*, 635–638.
42. Absolute configuration of the products was determined in comparison to the specific rotations in literature; otherwise, corresponding authentic samples were prepared using (*S*)-4-benzyl-2-oxazolidinone. Yields were calculated from the original loading of Wang resin.
43. This type of side reaction is known in the standard Evans' chemistry and thought that the enolate intermediate partially decomposes via a ketene-pathway, see Ref. 15.
44. (a) Carboxylic acid **26c** is known as a key component of α-chymotripsin inhibitor, see: Kim, D. H.; Li, Z.-H.; Lee, S. S.; Park, J.; Chung, S. J. *Bioorg. Med. Chem.* **1998**, *6*, 239–249. (b) Carboxylic acid **26e** is known as a key component of carboxypeptidase inhibitor, see: Byers, L. D.; Wolfenden, R. *Biochemistry* **1973**, *12*, 2070–2078. (c) Carboxylic acid **26i** and **26k** are known as a key acyl component of potent γ-secretase inhibitor, see: Churcher, I.; Ashton, K.; Butcher, J. W.; Clarke, E. E.; Harrison, T.; Lewis, H. D.; Owens, A. P.; Teall, M. R.; Williams, S.; Wrigley, J. D. J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 179–183.
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